

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 October 2002 (24.10.2002)

PCT

(10) International Publication Number
WO 02/082968 A2

(51) International Patent Classification⁷: **A61B** **Ophir** [IL/IL]; 49 Af Al Pi Chen Street, 30900 Zichron Yaacov (IL).

(21) International Application Number: **PCT/IL02/00309**

(22) International Filing Date: 16 April 2002 (16.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/284,497 18 April 2001 (18.04.2001) US

(71) Applicant (for all designated States except US): **IMPULSE DYNAMICS NV** [NL/NL]; 3 L.B. Smithplein, Cuzacau (AN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **POLICKER, Shai** [IL/IL]; 42810 Moshav Tzur Moshe (IL). **AVIV, Ricardo** [IL/IL]; 99 Einstein Street, 34601 Haifa (IL). **BITON,**

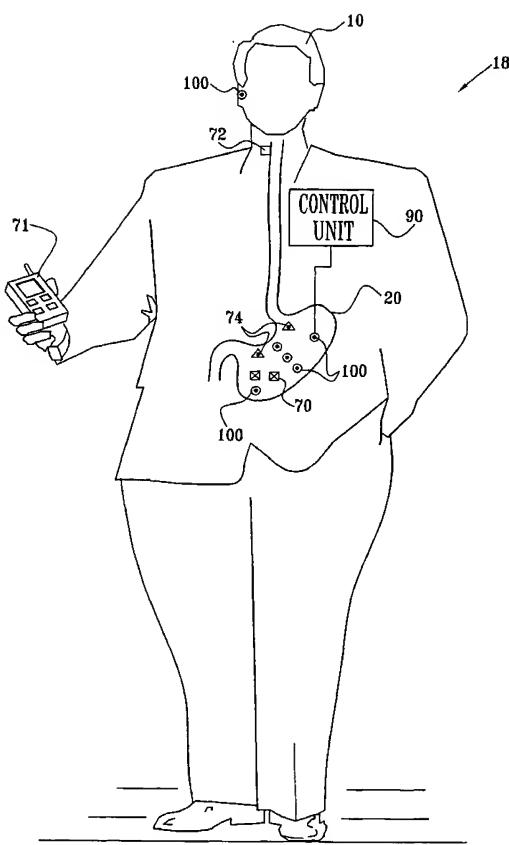
(74) Agents: **SANFORD T. COLB & CO.** et al.; P.O. Box 2273, 76122 Rehovot (IL).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent

[Continued on next page]

(54) Title: ANALYSIS OF EATING HABITS



(57) Abstract: Diet evaluation gastric apparatus (18) is provided, which detects when a patient (10) swallows, and detects the type and amount of matter ingested. The apparatus includes electrodes (74, 100) adapted to be coupled to the fundus and antrum of the patient and to measure electrical and mechanical activity therein, and a control unit (90) to analyze such electrical and mechanical activity and optionally apply electrical energy to modify the activity of tissue of the patient.

WO 02/082968 A2



(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- *without international search report and to be republished upon receipt of that report*

ANALYSIS OF EATING HABITS**FIELD OF THE INVENTION**

The present invention relates generally to tracking eating habits, and specifically to invasive techniques and apparatus for detecting and analyzing the 5 swallowing and digesting of food.

BACKGROUND OF THE INVENTION

Morbid obesity is a difficult to treat chronic condition defined by a body mass index (BMI = mass/height² [kg/m²]) greater than 40. For obese persons, excessive weight is commonly associated with increased risk of cardiovascular disease, 10 diabetes, degenerative arthritis, endocrine and pulmonary abnormalities, gallbladder disease and hypertension. Additionally, such persons are highly likely to experience psychological difficulties because of lifestyle restrictions such as reduced mobility and physical capacity, due to back pain, joint problems, and shortness of breath. In severe cases, this can contribute to absenteeism and unemployment. Moreover, 15 impairment of body image can lead to significant psychological disturbances. Repeated failures of dieting and exercise to resolve the problem of obesity can result in feelings of despair and the development of clinical depression.

Bariatric surgery is often recommended for persons suffering from morbid obesity. Preferably, the invasive treatment is accompanied by changes in lifestyle, 20 such as improved regulation of eating habits and an appropriate exercise regimen. Such lifestyle changes are dependent upon the self-discipline and cooperation of the patient.

A book entitled, *Textbook of Gastroenterology*, 3rd edition, edited by Yamada (Lippincott, Williams & Wilkins), which is incorporated herein by reference, has in 25 Chapter 10 thereof a description of the physiology of gastric motility and gastric emptying.

An abstract entitled, "Gastric myoelectrical pacing as therapy for morbid obesity: Preliminary results," by Cigaina et al., retrieved on December 24, 2000 from the Web-site <http://www.med-online.com / transneuronix / Product / abstract.htm>, 30 which is incorporated herein by reference, describes a method for applying monopolar and bipolar gastric stimulation to achieve weight loss.

An abstract entitled, "Implantable gastric stimulator (IGS) as therapy for morbid obesity: Equipment, surgical technique and stimulation parameters," by Cigaina et al., retrieved on December 24, 2000 from the Web-site <http://www.med-online.com / transneuronix / Product / abstract.htm>, which is incorporated herein by reference, describes techniques of electrical signal therapy designed to treat obesity.

US Patent 6,129,685 to Howard, which is incorporated herein by reference, describes apparatus and methods for regulating appetite by electrical stimulation of the hypothalamus and by microinfusion of an appropriate quantity of a suitable drug to a distinct site or region within the hypothalamus.

US Patent 4,823,808 to Clegg et al., which is incorporated herein by reference, describes a method for treating obesity, including receiving a physiological measurement and generating audio or visual feedback for the patient to hear or see. The feedback is used for purposes of teaching behavior modification.

US Patent 5,868,141 to Elias, which is incorporated herein by reference, describes an endoscopic stomach insert for reducing a patient's desire to eat.

US Patents 6,067,991 to Forsell, 5,601,604 to Vincent, 5,234,454 to Bangs, 4,133,315 to Berman et al., 4,416,267 to Garren et al., and US Patents 4,592,339, 5,449,368, 5,226,429 and 5,074,868 to Kuzmak, which are incorporated herein by reference, describe mechanical instruments for implantation in or around the stomach of an obese patient.

US Patent 5,690,691 to Chen et al., which is incorporated herein by reference, describes a gastric pacemaker for treating obesity and other disorders. The pacemaker includes multiple electrodes which are placed at various positions on the gastrointestinal (GI) tract, and deliver phased electrical stimulation to pace peristaltic movement of material through the GI tract.

US Patent 5,423,872 to Cigaina, which is incorporated herein by reference, describes apparatus for applying electrical pulses to the distal gastric antrum of a patient, so as to reduce the motility of the stomach and to thereby treat obesity or another disorder.

US Patents 5,188,104 and 5,263,480 to Wernicke et al., which are incorporated herein by reference, describe a method for stimulating the vagus nerve of a patient so as to alleviate an eating disorder.

US Patents 6,104,955, 6,091,992, and 5,836,994 to Bourgeois, 6,026,326 to Bardy, and 3,411,507 to Wingrove, which are incorporated herein by reference, describe the application of electrical signals to the GI tract to treat various physiological disorders.

5 US Patent 5,979,449 to Steer, which is incorporated herein by reference, describes an oral appliance for appetite suppression.

US Patent 4,975,682 to Kerr et al., which is incorporated herein by reference, describes apparatus for food intake regulation which is external to the body and which is based upon the voluntary cooperation of the subject in order to be effective.

10 US Patents 5,861,014 to Familoni, 5,716,385 to Mittal et al., and 5,995,872 to Bourgeois, are incorporated herein by reference, and describe methods and apparatus for stimulation of tissue, particularly gastrointestinal tract tissue.

15 PCT Patent Publication WO 98/10830 to Ben-Haim et al., entitled, "Fencing of cardiac muscles," and US Patent Application 09/254,903 in the national phase thereof, both of which are assigned to the assignee of the present patent application and are incorporated herein by reference, describe various methods for controlling the behavior of muscle tissue, for example by blocking or altering the transmission of signals therethrough.

20 PCT Patent Publication WO 99/03533 to Ben-Haim et al., entitled, "Smooth muscle controller," and US Patent Application 09/481,253 in the national phase thereof, both of which are assigned to the assignee of the present patent application and are incorporated herein by reference, describe apparatus and methods for applying signals to smooth muscle so as to modify the behavior thereof. In particular, apparatus for controlling the stomach is described in which a controller applies an 25 electrical field to electrodes on the stomach wall so as to modify the reaction of muscle tissue therein to an activation signal, while not generating a propagating action potential in the tissue. In the context of the present patent application and in the claims, the use of such a non-excitatory signal to modify the response of one or more cells to electrical activation thereof, without inducing action potentials in the cells, is 30 referred to as Excitable-Tissue Control (ETC). Use of an ETC signal is described in the PCT Patent Publication with respect to treating obesity, by applying the ETC signal to the stomach so as to delay or prevent emptying of the stomach. In addition,

a method is described for increasing the motility of the gastrointestinal tract, by applying an ETC signal to a portion of the tract in order to increase the contraction force generated in the portion.

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide apparatus and methods for detecting and tracking the swallowing of solids and liquids.

5 It is a further object of some aspects of the present invention to provide apparatus and methods for detecting, tracking, quantifying and determining the qualitative character of ingested liquids and solids.

It is still a further object of some aspects of the present invention to provide improved apparatus and methods for treating obesity.

10 It is yet a further object of some aspects of the present invention to provide apparatus and methods that enable the implementation of changes in food ingestion habits in a predictable and controlled manner.

It is an additional object of some aspects of the present invention to provide methods and apparatus for regulating food ingestion.

15 It is still an additional object of some aspects of the present invention to provide apparatus and methods for bariatric surgery that are less drastic than those currently employed.

In preferred embodiments of the present invention, apparatus for detecting, tracking, quantifying and determining the qualitative character of ingested liquids and solids comprises a sensor coupled to a patient's gastrointestinal tract. Preferably, the 20 sensor generates a signal indicative of the swallowing of food. An analysis module preferably determines a quality of the food, for example, whether it is predominantly solid or liquid, and stores this information in an electronic memory. Alternatively or additionally, the analysis module determines other characteristics of the ingested material, for example, the nutritional, chemical, and/or caloric content. "Food," as 25 used in the context of the present patent application and in the claims, is to be understood as including both solid and liquid food. "Swallowing," as used in the context of the present patent application and in the claims, is to be understood as being indicative of the onset of eating.

30 In some preferred embodiments of the present invention, swallowing is detected by tracking the electrical activity in muscle tissue in the fundic region of the stomach. Typically, the commencement of enhanced electrical activity is also

detected in muscle tissue in the antral region of the stomach. Measurement of the time delay between swallowing and the commencement of electrical activity in the antrum is preferably used to differentiate between solid and liquid matter, which are generally passed at different rates through the stomach.

5 Alternatively or additionally, swallowing is detected by at least one sensor placed at a site on the gastrointestinal tract other than the fundic region of the stomach, and the sensor generates a signal indicative of swallowing. Appropriate sites include, but are not limited to, a site on the esophagus, a site on the stomach, and a site on the throat. Whenever detection of swallowing is described in the present
10 patent application with respect to fundic activity, it is to be understood as being by way of example, and not as excluding detection by a sensor located elsewhere on the gastrointestinal tract.

15 Preferably, measurement of the intensity and/or duration of the electrical activity in the antral region is correlated with aspects of fundic electrical activity denoting swallowing, as described hereinbelow, such that ingested matter of differing chemical and nutritional content can be distinguished. Further preferably, the amount of food accumulated in the fundus or antrum is estimated by measuring a level of electrical activity at various sites in the stomach.

20 Typically, electrical activity response criteria of the stomach of an individual patient are determined and calibrated by measuring the response of the patient's stomach to various types of solid and liquid food. To ensure appropriate compliance, calibration is preferably performed under the supervision of a healthcare worker. For illustration, a table such as the following may be established for a particular patient. Except with respect to the example of sugarless chewing gum, these illustrative values
25 are shown with respect to a constant volume of food or liquid ingested (e.g., 100 ml or steak, water, or tomato juice).

TABLE I

Substance	Fundic activity level	Antral activity level	Time delay until onset of antral activity
Sugarless chewing gum	1	1	-
Non-caloric liquid - Water	2	1	-
Caloric liquid - Tomato juice	2	2	<1 Minute
Caloric liquid - Milk	2	2	<1 Minute
Solid - Apple	2	2	Minutes
Solid - Meat	2	3	Minutes

In this illustration, the measured data are preferably analyzed to determine signal characteristics which correspond to the indicated fundic and antral electrical activity levels. For example, calibration of fundic activity during the chewing of sugarless gum typically yields a low level indication of swallowing, while calibration during the swallowing of liquids and solids yields a greater fundic response. Similarly, there is typically no significant antral response to the patient drinking water, while calibration during the digestion of liquids and solids having higher caloric content yields a greater antral response. Measurements are preferably made of the delay time between swallowing and the commencement of antral activity, because consumption of liquids is typically characterized by a rapid transition from the fundus to the antrum, while solids typically stay in the fundus for at least about 10 minutes prior to being passed to the antrum. Preferably, a large variety of liquids and solids are used to establish a profile of electrical response characteristics for each patient.

For some applications, various supplemental sensors are also applied to the gastrointestinal tract or elsewhere on or in the patient's body. These supplemental sensors, which may comprise pH sensors, blood sugar sensors, ultrasound transducers or mechanical sensors, typically convey signals to a control unit of the apparatus

indicative of a characteristic of solids or liquids ingested by the patient. For example, an ultrasound transducer may be coupled to indicate whether ingesta are solid or liquid, and a pH sensor may indicate that an acidic drink such as tomato juice was consumed rather than a more basic liquid such as milk.

5 In a preferred embodiment, the collected data are stored and intermittently uploaded to an external computer, preferably by a wireless communications link, for review by the patient's physician, to enable monitoring of the patient's adherence to a dietary regimen.

10 For some applications, a specific schedule of allowed food ingestion is pre-programmed by the physician into the memory, and a processor is continuously operative to detect whether food consumption is taking place in accordance with the programmed schedule. For some patients, the schedule may be less strict with respect to drinking certain types of liquids, and more strict with respect to eating certain types of solid food. When an exception from the schedule is detected, the processor 15 preferably actuates a signal generator to convey an ingestion-control signal to the patient, in order to encourage the patient to adhere to the schedule. Preferably, but not necessarily, apparatus and methods described in US Provisional Patent Application 60/259,925, entitled, "Regulation of eating habits," filed January 5, 2001, and in a PCT patent application entitled, "Regulation of eating habits," filed in January, 2002, 20 both of which are assigned to the assignee of the present patent application and incorporated herein by reference, are utilized in the administration of the ingestion-control signal. Alternatively or additionally, the signal generator generates a visual, audio, or other cue or causes another reasonable discomfort to encourage the patient 25 to adhere to the schedule.

25 For embodiments in which this form of dietary monitoring is supplemented by dietary regulation, the apparatus preferably compares the indications of actual food and drink consumption with the pre-programmed schedule. In the event of a sufficient level of patient non-compliance, the ingestion-control signal is preferably delivered to the patient's stomach via a set of electrodes placed in a vicinity thereof, so 30 as to induce a sensation of discomfort or minor nausea. For example, an unpleasant sensation such as nausea may be induced by altering the natural electrical activity of the stomach, thereby inducing gastric dysrhythmia, or, alternatively, discomfort may be induced by pacing the rectus abdominus muscle.

Alternatively or additionally, the signal is applied to another site on or in the patient's body. For example, the ingestion-control signal may be applied mechanically or electrically in a vicinity of the cochlear nerve, so as to induce vertigo. Alternatively, the signal is applied so as to generate a brief pain sensation anywhere 5 on the patient's body, which only recurs if the patient continues to eat. Further alternatively, the signal is applied to the esophagus or to the lower esophageal sphincter, so as to cause contraction of muscle tissue therein, thereby making any further eating difficult or very uncomfortable.

Alternatively or additionally, the ingestion-control signal is configured so as to 10 induce a feeling of satiation, preferably but not necessarily in accordance with methods described in US Patent Application 09/734,358, entitled, "Acute and chronic electrical signal therapy for obesity," filed on December 21, 2000, which is assigned to the assignee of the present patent application and is incorporated herein by reference. For example, methods described in that application for engendering a 15 feeling of satiation may be applied in conjunction with embodiments of the present invention, such that muscles in the vicinity of stretch receptors in the stomach are caused to contract, thereby resulting in decreased hunger sensations. Alternatively or additionally, the feeling of satiation is induced by applying electrical signals which enhance the mobility of chyme from the fundus to the antrum of the stomach, where 20 stretch-receptor signals are generally generated to a greater extent for a given quantity of food than in the fundus.

In a preferred embodiment, when an exception from the schedule of allowed food ingestion is detected, the processor preferably conveys the exception to an 25 external operator control unit, which in turn wirelessly communicates the exception in real time to a remote computer system. The remote computer system can be configured to analyze the exception based on predetermined rules and, if necessary, perform an appropriate action, such as notification of a healthcare worker, care provider, or family member of the patient, in order to encourage the patient to adhere to the schedule.

30 Preferably, the schedule of allowed food ingestion can be modified after implantation of the apparatus, typically by means of a wireless communications link. In this manner, the schedule can be adjusted in response to changes in the patient's eating habits and experience with the apparatus.

There is therefore provided, in accordance with a preferred embodiment of the present invention, gastric apparatus, including:

5 a gastrointestinal sensor, adapted to be coupled to a gastrointestinal site of a subject and to generate a gastrointestinal sensor signal responsive to a property of the gastrointestinal site;

a set of one or more antral sensors, adapted to be coupled to an antral site of an antrum of the stomach and to generate an antral sensor signal responsive to a property of the antrum; and

10 a control unit, adapted to receive and analyze the gastrointestinal and antral sensor signals, and to determine, responsive thereto, a characteristic of a food ingested by the subject.

Preferably, the control unit is adapted to be implanted in the subject.

15 In a preferred embodiment, the characteristic of the ingested food includes a caloric content of the ingested food, and the control unit is adapted to determine the caloric content. Alternatively or additionally, the characteristic of the ingested food includes a chemical content of the ingested food, and the control unit is adapted to determine the chemical content. Further alternatively or additionally, the characteristic of the ingested food includes a nutritional content of the ingested food, and the control unit is adapted to determine the nutritional content.

20 For some applications, the apparatus includes an operator unit, which is adapted to be disposed external to the subject and to transmit a control signal to the control unit.

25 In a preferred embodiment, the gastrointestinal sensor is adapted to generate a swallowing sensor signal responsive to swallowing by the subject. Typically, the gastrointestinal sensor is adapted to be placed at an esophageal site of the subject, a site of the stomach of the subject, and/or a site of a throat of the subject.

30 Preferably, the gastrointestinal sensor includes a set of one or more fundic sensors, adapted to be coupled to a fundic site of a fundus of the stomach of the subject and to generate a fundic sensor signal responsive to a property of the fundus, and the control unit is adapted to receive and analyze the fundic and antral sensor signals, and to determine, responsive thereto, the characteristic of the ingested food.

In a preferred embodiment, the fundic sensor set includes one or more strain gauges. Alternatively or additionally, the antral sensor set includes one or more strain gauges.

Typically, the fundic sensor set includes a set of fundic electrodes, adapted to generate a fundic electrode signal responsive to a property of the fundus, the antral sensor set includes a set of antral electrodes, adapted to generate an antral electrode signal responsive to a property of the antrum, and the control unit is adapted to receive and analyze the fundic and antral electrode signals, and to determine, responsive thereto, the characteristic of the ingested food. For example, the control unit may be adapted to determine, responsive to an analysis of at least one of the electrode signals, an amount of the ingested food accumulated in a region of the stomach. Alternatively or additionally, the control unit is adapted to count, responsive to an analysis of at least one of the electrode signals, a number of meals ingested by the subject during a period of time.

The antral electrode set typically includes two antral electrodes, adapted to be coupled to two sites of the antrum, and the control unit is adapted to identify a measure of electrical impedance between the two sites of the antrum. In this case, the control unit is preferably adapted to determine the characteristic of the ingested food, responsive to a change in the measure of electrical impedance. For some applications, the fundic electrode set includes two fundic electrodes, adapted to be coupled to two sites of the fundus, and the control unit is adapted to identify a measure of electrical impedance between the two sites of the fundus. For example, the control unit may be adapted to determine the characteristic of the ingested food, responsive to a change in the measure of electrical impedance. Alternatively or additionally, the control unit is adapted to identify an increased measure of electrical impedance relative to a baseline value as indicative of eating. Further alternatively or additionally, the control unit is adapted to identify a substantial return towards a baseline value of the measure of electrical impedance as indicative of a termination of eating.

For some applications, the control unit is adapted to identify an increase in the measure of electrical impedance as indicative of an onset of eating. For example, the control unit may be adapted to detect the onset of eating, responsive to the increase in the measure of electrical impedance being greater than 5 ohms per centimeter of distance between the two sites of the fundus.

In a preferred embodiment, the control unit is adapted to perform a calibration including measurement of a response of the fundic and antral electrode signals to ingestion by the subject of one or more test foods. For example, the one or more foods may include one or more solid foods, and the control unit may be adapted to 5 perform the calibration responsive to ingestion of the one or more solid foods. Alternatively or additionally, the one or more foods includes one or more liquid foods, and the control unit is adapted to perform the calibration responsive to ingestion of the one or more liquid foods. Further alternatively or additionally, the one or more foods includes one or more solid foods and one or more liquid foods, and herein the control 10 unit is adapted to perform the calibration responsive to ingestion of the one or more solid foods and the one or more liquid foods.

In a preferred embodiment, the antral electrode set is adapted to generate the antral electrode signal responsive to an electrical potential change generated responsive to a contraction of a muscle of the antrum. In this case, the control unit is 15 preferably adapted to determine, responsive to an amplitude of the antral electrode signal, the characteristic of the ingested food. Alternatively or additionally, the control unit is adapted to determine, responsive to a frequency of the antral electrode signal, the characteristic of the ingested food. Further alternatively or additionally, the control unit is adapted to determine, responsive to a spike energy per antral cycle 20 of electrical activity, the characteristic of the ingested food. Still further alternatively or additionally, the control unit is adapted to determine, responsive to a duration of the antral electrode signal, the characteristic of the ingested food.

In a preferred embodiment, the control unit is adapted to determine, responsive to a change in a rate of antral electrode signal events, the characteristic of the ingested 25 food. The control unit may alternatively or additionally be adapted to identify an increase in an amplitude of the antral electrode signal as indicative of an onset of a cephalic phase occurring in the subject. For some applications, the control unit is adapted to identify an increase in an amplitude of the antral electrode signal as indicative of an onset of antral digestion. Alternatively or additionally, the control 30 unit is adapted to identify a reduction in a rate of antral electrode signal events as indicative of an onset of antral digestion.

For some applications, the control unit is adapted to identify an increased amplitude of the antral electrode signal relative to a baseline value as indicative of

antral digestion. Alternatively or additionally, the control unit is adapted to identify a reduced rate of antral electrode signal events relative to a baseline value as indicative of antral digestion. Further alternatively or additionally, the control unit is adapted to identify a substantial return towards a baseline value of an amplitude of the antral 5 electrode signal as indicative of a termination of antral digestion. Still further alternatively or additionally, the control unit is adapted to identify a substantial return towards a baseline value of a rate of antral electrode signal events as indicative of a termination of antral digestion.

The control unit is preferably adapted to determine the characteristic of the 10 ingested food, responsive to a time delay between an onset of eating and an onset of a decreased rate of electrical events in the antrum. For some applications, the control unit is adapted to determine the characteristic of the ingested food, responsive to the time delay and responsive to a threshold time delay. Alternatively or additionally, the control unit is adapted to determine, responsive to the time delay, an extent to which 15 the ingested food includes solid food matter. In this case, the control unit is preferably adapted to determine that the ingested food includes solid food matter, responsive to the time delay being more than about one minute. For some applications, the control unit is adapted to determine that the ingested food includes predominantly solid food matter, responsive to the time delay being more than about 5 20 minutes.

In a preferred embodiment, the control unit is adapted to determine, responsive to the time delay, an extent to which the ingested food includes liquid food matter. For example, the control unit may be adapted to determine that the ingested food includes liquid food matter, responsive to the time delay being less than about 5 25 minutes. Alternatively or additionally, the control unit is adapted to determine that the ingested food includes predominantly liquid food matter, responsive to the time delay being less than about one minute.

For some applications, the control unit is adapted to determine the characteristic of the ingested food, responsive to a time delay between an onset of 30 eating and an onset of increased electrical activity in the antrum. In this case, the control unit is preferably adapted to determine the characteristic of the ingested food, responsive to the time delay and responsive to a threshold time delay. Further preferably, the control unit is adapted to determine, responsive to the time delay, an

extent to which the ingested food includes solid food matter. For example, the control unit may be adapted to determine that the ingested food includes solid food matter, responsive to the time delay being more than about one minute. Alternatively or additionally, the control unit may be adapted to determine that the ingested food 5 includes predominantly solid food matter, responsive to the time delay being more than about 5 minutes. In a preferred embodiment, the control unit is adapted to determine, responsive to the time delay, an extent to which the ingested food includes liquid food matter. For example, the control unit may be adapted to determine that the ingested food includes liquid food matter, responsive to the time delay being less than 10 about 5 minutes. Alternatively or additionally, the control unit is adapted to determine that the ingested food includes predominantly liquid food matter, responsive to the time delay being less than about one minute.

Preferably, the fundic electrode set is adapted to generate the fundic electrode signal responsive to an electrical potential change generated responsive to a 15 contraction of a muscle of the fundus. For example, the control unit may be adapted to determine the characteristic of the ingested food responsive to an amplitude of the fundic electrode signal, a frequency of the fundic electrode signal, a duration of the fundic electrode signal, and/or a change in a rate of fundic electrode signal events of the fundic electrode signal.

20 In a preferred embodiment, the control unit is adapted to identify an increased amplitude of the fundic electrode signal relative to a baseline value as indicative of eating. Alternatively or additionally, the control unit is adapted to identify an increased frequency of the fundic electrode signal relative to a baseline value as indicative of eating. Further alternatively or additionally, the control unit is adapted 25 to identify a substantial return towards a baseline value of an amplitude of the fundic electrode signal as indicative of a termination of eating. Still further alternatively or additionally, the control unit is adapted to identify a substantial return towards a baseline value of a frequency of the fundic electrode signal as indicative of a termination of eating. For some applications, the control unit is adapted to identify an 30 increase in an amplitude of the fundic electrode signal as indicative of an onset of eating. For example, the control unit may be adapted to detect the onset of eating responsive to the increase in the amplitude of the fundic electrode signal being greater than about 20 percent.

In a preferred embodiment, the control unit is adapted to identify an increase in a frequency of the fundic electrode signal as indicative of an onset of eating. For example, the control unit may be adapted to detect the onset of eating, responsive to the increase in the frequency being greater than about 10 percent.

5 In a preferred embodiment, the control unit includes a memory, adapted to store a result of the analysis performed by the control unit. Preferably, the memory is adapted to upload the stored result to an external computer, e.g., by using a wireless communications link.

In a preferred embodiment, the apparatus includes a supplemental sensor 10 adapted to be placed at a site of the subject and to convey a supplemental sensor signal to the control unit. The control unit is preferably adapted to receive and analyze the supplemental sensor signal, and to determine, responsive thereto, the characteristic of the ingested food. Alternatively or additionally, the control unit is adapted to receive and analyze the supplemental sensor signal, and to determine, 15 responsive thereto, an onset of eating by the subject. Further alternatively or additionally, the control unit is adapted to receive and analyze the supplemental sensor signal, and to determine, responsive thereto, eating by the subject. Still further alternatively or additionally, the control unit is adapted to receive and analyze the supplemental sensor signal, and to determine, responsive thereto, a termination of 20 eating by the subject. Preferably, the supplemental sensor includes an electrode, a pH sensor, a blood sugar sensor, an ultrasound transducer, and/or a mechanical sensor. in a preferred embodiment, the supplemental sensor is adapted to be placed at a gastrointestinal site of the subject, an esophageal site of the subject, a site of the stomach of the subject, and/or a site of a throat of the subject.

25 For some applications, the control unit includes a memory, adapted to store a schedule of allowed food ingestion, wherein the apparatus includes an operator unit, which is adapted to be disposed external to the subject, and wherein the operator unit is adapted to generate an external cue when the analysis performed by the control unit is indicative of the subject not eating in accordance with the ingestion schedule. For 30 example, the external cue may include a visual cue, and the operator unit is adapted to generate the visual cue. Alternatively or additionally, the external cue includes an audio cue, and the operator unit is adapted to generate the audio cue. For some applications, the operator unit includes a user override, adapted to be used by the

subject and adapted to disable the cue. Alternatively or additionally, the operator unit is adapted to modify the schedule stored in the memory. For example, the operator unit may be adapted to modify the schedule responsive to information obtained by the operator unit, e.g., via a wireless communications link.

5 In a preferred embodiment, the apparatus includes a set of one or more current-application electrodes, adapted to be coupled to a tissue of the subject, and wherein the control unit is adapted to drive a current, responsive to the analysis, through the set of current-application electrodes into the tissue. For example, the current-application electrode set may be adapted to be placed at an aural site of the
10 subject, at an esophageal site of the subject, and/or at a site of the stomach of the subject. For some applications, the control unit is adapted to drive the current into the tissue responsive to the characteristic of the ingested food. In a preferred embodiment, the control unit is adapted to apply a pacing signal to a rectus abdominus muscle of the subject. For some applications, the control unit is adapted to drive the
15 current into the tissue responsive to a time of the subject eating.

In a preferred embodiment, the control unit is adapted to configure the current such that driving the current induces gastric dysrhythmia. Alternatively or additionally, the control unit is adapted to configure the current such that driving the current disrupts coupling of gastric mechanical activity and gastric electrical activity
20 of the subject. Further alternatively or additionally, the control unit is adapted to configure the current such that driving the current induces a sensation of discomfort in the subject. Still further alternatively or additionally, the control unit is adapted to configure the current such that driving the current induces a sensation of nausea in the subject. Yet further alternatively or additionally, the control unit is adapted to
25 configure the current such that driving the current induces a sensation of vertigo in the subject.

In a preferred embodiment, the control unit is adapted to drive the current-application electrode set to apply an Excitable-Tissue Control (ETC) signal to the tissue. For example, the control unit may be adapted to drive the current-application electrode set to apply a stimulatory pulse at a site of application of the ETC signal.
30 Alternatively or additionally, the control unit is adapted to drive the current-application electrode set to apply a stimulatory pulse to tissue at a site other than a site of application of the ETC signal. Still further alternatively or additionally, the control

unit is adapted to drive the current-application electrode set to apply the ETC signal in order to increase an aspect of contraction of the tissue. For some applications, the control unit is adapted to drive the current-application electrode set to apply the ETC signal in order to cause tissue contraction in a first portion of the stomach of the 5 subject, and stretching of a stretch receptor of the stomach in a second portion of the stomach. Alternatively or additionally, the control unit is adapted to drive the current-application electrode set to apply the ETC signal in order to increase a contraction strength of tissue in a vicinity of a stretch receptor of the stomach of the subject, so as to increase a sensation of satiation of the subject. Further alternatively or additionally, 10 the control unit is adapted to drive the current-application electrode set to apply the ETC signal to the tissue so as to enhance movement of chyme from a fundus to the antrum of the stomach of the subject.

In a preferred embodiment, the control unit includes a memory, adapted to store a schedule of allowed food ingestion, and wherein the control unit is adapted to 15 withhold driving the current when the analysis performed by the control unit is indicative of the subject eating in accordance with the ingestion schedule. Preferably, the ingestion schedule includes types of foods and associated amounts permitted during a time period, and the control unit is adapted to withhold driving the current when the analysis is indicative of the subject eating in accordance with the ingestion 20 schedule. Alternatively or additionally, the ingestion schedule includes a number of meals permitted during a time period, and the control is adapted to withhold driving the current when the analysis is indicative of the subject eating in accordance with the ingestion schedule. Further alternatively or additionally, the ingestion schedule includes an amount of food permitted at a certain meal, and the control is adapted to 25 withhold driving the current when the analysis is indicative of the subject eating in accordance with the ingestion schedule.

Preferably, the memory is adapted to download a new schedule from an external computer. For some applications, the apparatus includes an operator unit, which is adapted to be disposed external to the subject and to transmit a control signal 30 to the control unit. Further preferably, the operator unit includes a user override, adapted to be used by the subject and adapted to withhold driving the current.

There is further provided, in accordance with a preferred embodiment of the present invention, a method for analyzing gastric function of a stomach of a subject, including:

- 5 sensing a property of a gastrointestinal tract of the stomach;
- sensing a property of an antrum of the stomach;
- analyzing the property of the gastrointestinal tract and the property of the antrum; and
- determining, responsive to the analysis, a characteristic of a food ingested by the subject.

10 The present invention will be more fully understood from the following detailed description of the preferred embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustration of apparatus for treating obesity, in accordance with a preferred embodiment of the present invention;

5 Fig. 2 is a schematic block diagram showing a control unit of the apparatus of Fig. 1, in accordance with a preferred embodiment of the present invention;

Fig. 3 is a schematic diagram showing experimental apparatus used to measure electrical responses to eating in the stomach of a normal rabbit, in accordance with a preferred embodiment of the present invention;

10 Fig. 4 is a graph showing electrical activity in the fundus of a normal rabbit before and during eating, and results of analysis thereof, in accordance with a preferred embodiment of the present invention;

Figs. 5A is a graph showing electrical activity in the fundus of a normal rabbit during and following eating, and results of analysis thereof, in accordance with a preferred embodiment of the present invention;

15 Fig. 5B is a graph showing details of electrical and mechanical activity recorded during the taking of the data shown in Fig. 5A;

Fig. 6 is a graph showing detail of electrical fundic activity, measured in accordance with a preferred embodiment of the present invention;

20 Fig. 7 is a graph showing the rate of electrical events in the antrum of a normal dog before and during eating, and results of analysis thereof, in accordance with a preferred embodiment of the present invention;

Fig. 8 is a graph showing the rate of electrical events in the antrum of a normal dog before, during, and after eating, and results of analysis thereof, in accordance with a preferred embodiment of the present invention;

25 Fig. 9 is a graph showing electrical and mechanical activity and the rate of electrical events in the antrum of a normal dog before, during, and after eating, and results of analysis thereof, in accordance with a preferred embodiment of the present invention; and

Fig. 10 is a graph showing fundic electrical activity in a normal dog during several periods of eating and non-eating, and results of analysis thereof, in accordance with a preferred embodiment of the present invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 is a schematic illustration of diet evaluation apparatus 18, which detects when a patient 10 swallows, and detects the type and amount of matter ingested, in accordance with a preferred embodiment of the present invention. Preferably, but not necessarily, apparatus 18 additionally determines, responsive to the detection, whether to apply electrical energy to modify the activity of tissue of patient 10. Apparatus 18 typically comprises mechanical sensors 70, supplemental sensors 72, local sense electrodes 74, operator controls 71, and one or more current-application electrodes 100.

10 Electrodes 74 and 100 are typically coupled to the serosal layer of a stomach 20 and/or inserted into the muscular layer of the stomach in the fundic and antral regions. Alternatively or additionally, the electrodes are coupled elsewhere on the stomach, gastrointestinal tract, or to other suitable locations in or on the patient's body. The number of electrodes and sensors, as well as the positions thereof, are 15 shown in Fig. 1 by way of example, and other sites on stomach 20 or in or on the patient's body are appropriate for electrode and sensor placement in other applications of the present invention. Different types of electrodes known in the art are typically selected based on the specific condition of the patient's disorder, and may comprise stitch, coil, screw, patch, basket, needle and/or wire electrodes, or substantially any 20 other electrode known in the art of electrical stimulation or sensing in tissue.

Preferably, apparatus 18 is implanted in patient 10 in a manner generally similar to that used to implant gastric pacemakers or other apparatus for stimulating or sensing in the gastrointestinal tract that are known in the art. As appropriate, techniques described in one or more of the references cited in the Background section 25 of the present patent application may be adapted for use with these embodiments of the present invention. Other methods and apparatus useful in carrying out some embodiments of the present invention are described in the above-cited US Provisional Patent Application 60/259,925, entitled, "Regulation of eating habits," filed on January 5, 2001, and in the above-cited PCT patent application and in the above-cited 30 US Patent Application 09/734,358, entitled, "Acute and chronic electrical signal therapy for obesity," filed on December 11, 2000, which are assigned to the assignee of the present patent application and are incorporated herein by reference.

Fig. 2 is a schematic block diagram illustrating details of operation of a control unit 90 of apparatus 18, in accordance with a preferred embodiment of the present invention. Preferably, control unit 90 is implanted in patient 10, and receives signals from mechanical sensors 70, supplemental sensors 72, and local sense electrodes 74, 5 all of which are typically implanted on the gastrointestinal tract of the patient or elsewhere on or in the body of the patient. These sensors and electrodes are preferably adapted to provide an "ingestion activity analysis" block 80 of the control unit with information about food ingestion and/or the present state of the stomach.

Preferably, using techniques described hereinbelow, analysis block 80 10 determines each time that the patient swallows, and also the character and amount of the ingested matter. For example, local sense electrodes 74 coupled to the fundus of the stomach may send signals indicative of fundic electrical activity to analysis block 80, and analysis block 80 identifies aspects of these signals which are characteristic of swallowing of food by the patient. Additionally, mechanical sensors 70 and local 15 sensor electrodes 74 coupled to the corpus and antral regions of the stomach preferably send signals which analysis block 80 identifies as indicative of the onset, duration, and/or intensity of the digestive process in those regions. Preferably, these data are utilized by analysis block 80 to determine a quality of the ingested matter, for example, whether it is predominantly solid or liquid. Alternatively or additionally, 20 these data may be used to determine other characteristics of the ingested material, for example, its nutritional, chemical, and/or caloric content.

In a preferred embodiment, analysis block 80 determines the time delay 25 between swallowing (as measured, preferably, by local sense electrodes 74 on the fundus) and the commencement of electrical and mechanical activity in the antrum. This delay is typically used to differentiate between the ingestion of solid and liquid matter, because solids are generally held in the fundus for at least about 10 minutes before being passed to the antrum, while liquids are generally passed to the antrum essentially immediately.

Alternatively or additionally, the amount of food accumulated in the various 30 regions of stomach 20 is estimated by measuring a level of electrical or mechanical activity in a vicinity of those regions. Further alternatively or additionally, analysis block 80 processes data from supplemental sensors 72 indicative of the blood sugar

level of the patient, to enable an evaluation of whether and of what type of food has been ingested.

In order to improve the accuracy of the analyses described hereinabove, analysis block 80 is preferably calibrated by measuring the appropriate electrical response criteria of stomach 20 of patient 10 to various types of solid and liquid food. 5 To ensure appropriate compliance, calibration is preferably performed under the supervision of a healthcare worker.

For some applications, analysis block 80 stores the results of its analysis in a memory block 88 of control unit 90, and these results are later uploaded to an external 10 computer, preferably by a wireless communications link, for review by the patient's physician. Alternatively or additionally, analysis block 80 conveys results of its analysis of the inputs from mechanical sensors 70, supplemental sensors 72, and local sense electrodes 74, to a "parameter search and tuning" block 84 of control unit 90. Block 84 preferably evaluates the analysis performed by analysis block 80 with 15 respect to a pre-programmed or variable ingestion schedule stored in memory block 88, so as to determine whether the patient is eating in compliance with the schedule. Preferably, the schedule can be modified after implantation of control unit 90, by communication from operator controls 71 using methods described hereinbelow. If it is determined that the patient's eating is not in compliance with the schedule (e.g., the 20 patient has eaten too much at one meal, or has eaten too many meals in a day, or has had too much of a certain type of food or drink), then block 84 preferably actuates a signal generator block 86 to generate electrical signals that are applied by current-application electrodes 100 to tissue of patient 10. Block 86 preferably comprises 25 amplifiers, isolation units, and other standard circuitry known in the art of electrical signal generation.

The signals generated by block 86 are preferably configured so as to induce a response appropriate for controlling the patient's eating habits. For example, block 86 may drive current-application electrodes 100 to apply signals to the stomach that induce gastric dysrhythmia and the resultant feeling of discomfort or nausea. 30 Alternatively or additionally, the signals are applied to an aural site of patient 10 (e.g., in a vicinity of the cochlear nerve or the tympanic membrane), and are configured to induce vertigo, or another unpleasant balance-related sensation. Alternatively or

additionally, block 86 generates a visual, audio, or other cue to encourage the patient to adhere to the schedule.

For some applications, control unit 90 drives electrodes 100 to apply a modulation signal to muscle in one area of stomach 20, so as to induce a contraction 5 of the stimulated muscle that, in turn, induces satiety when food in an adjacent area of the stomach causes additional stretching of stretch-receptors therein. This signal may be applied in addition to or instead of the signals described hereinabove that produce gastric or other discomfort. The form of contraction-mediated stretching utilized in these applications simulates the normal appetite-reduction action of the stomach's 10 stretch-receptors, without the patient having eaten the quantities of food which would normally be required to trigger this appetite-reduction response. In a preferred application, current-application electrodes 100 are placed around the body of the stomach and are driven to induce a generally steady-state contraction of the corpus, which simulates electrically the squeezing of the corpus produced mechanically by 15 implanted gastric bands known in the art.

Preferably, the signals applied by current-application electrodes 100 include, as appropriate, an Excitable-Tissue Control (ETC) signal and/or an excitatory signal that induces contraction of muscles of the stomach. Aspects of ETC signal application are typically performed in accordance with techniques described in the 20 above-referenced PCT Publications WO 99/03533 and WO 97/25098 and their corresponding US national phase applications 09/481,253 and 09/101,723, *mutatis mutandis*.

Preferably, evaluation apparatus 18 includes remote operator controls 71, external to the patient's body. This remote unit is typically configured to enable the 25 patient or his physician to change parameters of the ingestion schedule stored in memory block 88. For example, if the patient has lost weight, the physician may change the ingestion schedule to allow a single mid-afternoon snack. Alternatively or additionally, operator controls 71 comprise an override button, so that the patient may eat outside of the designated meal times, or consume a particular food or drink not in 30 accordance with the schedule, if the need arises. Operator controls 71 preferably communicate with control unit 90 using standard methods known in the art, such as magnetic induction or radio frequency signals.

Fig. 3 is a schematic diagram showing experimental apparatus 60 used to measure electrical responses to eating in the stomach 64 of a normal rabbit, in accordance with a preferred embodiment of the present invention. Bipolar sense electrodes 62 were coupled to the fundus of stomach 64, and bipolar sense electrodes 5 63 were coupled to the antrum of the stomach. Additionally, two stitch electrodes 66 with a strain gauge 68 located therebetween were coupled to the antrum.

Reference is now made to Figs. 4, 5A and 5B, which are graphs showing the results of experiments performed using apparatus 60 in a rabbit, in accordance with a preferred embodiment of the present invention. Fig. 4 shows electrical activity in the 10 fundus, measured during a five minute period before the rabbit was fed solid food, and during a more than six minute period while the rabbit was eating solid food. It can be seen that the second period is distinguished by markedly increased electrical activity. Spikes, typified by those marked "A," "B," and "C" in this graph, are preferably identified by a control unit operating in accordance with these 15 embodiments of the present invention, and are interpreted as indications of eating. It is noted that in the case of the rabbit experiment shown in Fig. 4, electrical activity as measured by spikes per unit time increased by a factor of about 8, and is therefore considered to be a good indication of the initiation and continuation of eating.

Fig. 5A is a graph showing the electrical response of the fundus of the rabbit 20 stomach, and the results of analysis thereof, in accordance with a preferred embodiment of the present invention. In this experiment, the measurements were first taken for five minutes while the rabbit was eating solid food, and were continued for almost 10 minutes after the rabbit ceased eating. It is clearly seen that the period after the rabbit ate is characterized by significantly less electrical activity than that which 25 occurred during eating. Spikes, such as those marked "A," "B," and "C" in this graph, occur at a rate at least 15 times higher during eating than thereafter, and are therefore preferably used by a control unit to determine both the onset and the termination of eating.

Fig. 5B is an expanded view of some of the data shown in Fig. 5A, 30 additionally showing simultaneous mechanical and electrical activity in the antrum of the rabbit. The top graph shows mechanical activity in the antrum as measured by strain gauge 68 (Fig. 3), and the middle graph shows electrical activity in the antrum, measured by electrodes 63 during the same time period. The repeated co-occurrence

of antral mechanical and electrical activity, as seen in Fig. 5B, is indicative of the expected antral mechanical response to antral electrical activity.

The bottom graph of Fig. 5B shows the measured electrical activity in the fundus during the same period, i.e., while the rabbit was eating. It can be seen that, 5 while there is close correlation between mechanical and electrical activity in the antrum, there is no correlation seen between fundic electrical activity and either measure of antral activity. Control unit 90 (Fig. 2) is therefore generally enabled to measure and differentiate between fundic and antral response, and to utilize this information to facilitate the evaluations and determinations described herein.

10 Fig. 6 is a graph showing electrical impedance measurements made between two stitch electrodes placed in the stomach of a pig, in accordance with a preferred embodiment of the present invention. In this experiment, fundic volume was measured at the same time as the impedance was measured, and the data show a clear dependence of the impedance on the volume. It is hypothesized that as the fundus 15 distends, the fundic wall thickness decreases, producing a corresponding increase in electrical impedance. Alternatively or additionally, the increased distance between the two electrodes produced as a result of the distension causes the electrical impedance to increase. Similar experimental results (not shown) were obtained when impedance and volume measurements were made in the antrum. Moreover, changes 20 in impedance were found to correlate with waves of antral activity.

Reference is now made to Figs. 7, 8, 9, and 10, which are graphs showing the results of experiments performed using apparatus (not shown) similar to apparatus 60 in several normal dogs, in accordance with a preferred embodiment of the present invention. All of the dogs fasted for approximately 24 hours prior to eating during the 25 experiments.

Fig. 7 shows the rate of electrical events in the antrum in a dog, measured during a six minute period before the dog was fed solid food and during a more than seven minute period while the dog was eating solid food. Electrical events that were recorded were spikes in the signal of amplitude at least a threshold amount greater 30 than the signal noise. It will be appreciated that detecting changes in other events may be useful for some applications. It will also be appreciated that whereas data shown in the figures reflects measurements of antral electrical events, for some

applications the analysis techniques described herein may also be implemented with respect to the rate of fundic electrical events.

It can be seen that the second period is distinguished by a markedly decreased rate of antral electrical events. Such a decrease is preferably identified by a control 5 unit operating in accordance with these embodiments of the present invention, and is interpreted as an indication of eating. It is noted that the rate of antral electrical events, as measured by events per unit time, decreased on average by about 20% beginning about one minute after the initiation of eating, and is therefore considered to be a good indication of the initiation and continuation of eating. (Decreases of up 10 to about 50% were seen in other experiments.) Alternatively or additionally, responsive to a calibration procedure, such a decrease in the rate of antral electrical events may be used to determine other characteristics of the ingested material, for example, its nutritional, chemical, and/or caloric content. Similar results were obtained in experiments on two other dogs (not shown).

15 Fig. 8 is a graph showing the rate of electrical events in the antrum in a second dog, measured during a more than 40 minute period before the dog was fed solid food, during an approximately 13 minute period while the dog was eating solid food (interrupted by an approximately 6 minute period of non-eating), and during an almost 60 minute period after the dog ceased eating. It is clearly seen that the period 20 beginning approximately four minutes after the dog ceased eating is characterized by return to a rate of antral electrical events almost equal to the rate prior to eating, and significantly higher than the reduced rate during eating. The rate of antral electrical events is therefore preferably used by a control unit to determine both the onset and the termination of antral activity.

25 Fig. 9 is a graph showing simultaneous mechanical activity, electrical activity, and rate of electrical events in the antrum of a third dog, measured during a more than 16 minute period before the dog was fed solid food, during an approximately 3.5 minute period while the dog was eating solid food, and during a more than four minute period after the dog ceased eating. The top graph shows mechanical activity 30 in the antrum as measured by a strain gauge, and the middle graph shows electrical activity in the antrum, measured by electrodes during the same time period. It can be seen that co-occurring mechanical and electrical activity began approximately 1.5

minutes prior to the beginning of eating, corresponding with the onset of cephalic phase activity (brain activity reflecting the mental anticipation of eating).

The bottom graph of Fig. 9 shows the rate of electrical events in the antrum of the dog. It can be seen that the second period is distinguished by a markedly 5 decreased rate of antral electrical events, consistent with the results of the first dog experiment described hereinabove. An increase in mechanical and/or electrical antral activity prior to eating as occurred in this experiment is preferably identified by a control unit operating in accordance with these embodiments of the present invention, and provides additional information that can be interpreted together with information 10 such as the decreased rate of antral electrical events observed in this experiment to provide indications of anticipation of eating, eating and/or gastric digestion.

Fig. 10 is a graph showing electrical impedance measurements made between two stitch electrodes in the fundus of a fourth dog, measured during five sequential periods: (1) an approximately 22 minute period before the dog was fed solid food 15 (portion of period not shown), (2) an approximately three minute period while the dog was eating solid food, (3) an approximately 7.5 minute period during which the dog did not eat, (4) an approximately one minute period while the dog was eating solid food, and (5) a greater than 10 minute period after the dog ceased eating.

It can be seen that the eating periods (second and fourth periods) are 20 distinguished by markedly increased fundic electrical impedance. Such increases are preferably identified by a control unit operating in accordance with these embodiments of the present invention, and are interpreted as indications of eating. This interpretation is supported by the correlation between impedance and volume measurements in the fundus obtained in the pig experiments described hereinabove. It 25 is noted that in the case of the dog experiment shown in Fig. 10, the fundic electrical impedance, as measured in ohms, increased by more than about 12%, beginning less than about one minute after the initiation of eating during the second period, and by about 5% beginning less than about one minute after the initiation of eating during the fourth period. The fundic electrical impedance is therefore considered to be a good 30 indication of the initiation and continuation of eating. Similar results were obtained in two other experiments on different days on the same dog (not shown).

It is clearly seen in Fig. 10 that the period beginning almost immediately after the dog ceased eating (the fifth period) is characterized by a return of fundic electrical impedance to a value almost equal to that prior to eating, and significantly lower than the increased value observed during eating. Fundic electrical impedance is therefore 5 preferably used by a control unit to determine both the onset and the termination of eating.

The inventors have observed that fundic electrical impedance (e.g., as measured in the case of the dog experiment shown in Fig. 10), as an indicator of eating, typically exhibits lower variability than antral electrical impedance, and is less 10 affected by movement and/or change in posture of the subject. Fundic electrical impedance also typically provides more reliable detection of eating than antral activity.

In preferred embodiments of the present invention, measurements of antral and/or fundic electrical impedance are used in conjunction with or separately from 15 other indicators of swallowing or digestion, described hereinabove, in order to track a patient's eating habits. Advantageously, impedance measurements made between two electrodes located even at mutually remote sites on a portion of the stomach can be accurate indicators of global strain of that portion, while a mechanical strain gauge placed at a particular site on the stomach generally only yields an indication of strain 20 at that site.

It will be recognized by persons skilled in the art that more complex combinations of variations in levels of electrical or mechanical activity in different regions of the stomach may occur than those demonstrated in the experiments described hereinabove. For example, certain electrical or mechanical activity may lag 25 the eating of certain amounts and types of food. Examples of more complex combinations (not shown) were obtained in additional experiments in other dogs. Analysis block 80, with proper calibration as described hereinabove, can readily be enabled to evaluate such complex combinations.

It will be appreciated by persons skilled in the art that the present invention is 30 not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove, as well as variations and modifications

thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.

CLAIMS

1. Gastric apparatus, comprising:
 - a gastrointestinal sensor, adapted to be coupled to a gastrointestinal site of a subject and to generate a gastrointestinal sensor signal responsive to a property of the gastrointestinal site;
 - a set of one or more antral sensors, adapted to be coupled to an antral site of an antrum of the stomach and to generate an antral sensor signal responsive to a property of the antrum; and
- 10 a control unit, adapted to receive and analyze the gastrointestinal and antral sensor signals, and to determine, responsive thereto, a characteristic of a food ingested by the subject.
2. Apparatus according to claim 1, wherein the control unit is adapted to be implanted in the subject.
- 15 3. Apparatus according to claim 1, wherein the characteristic of the ingested food includes a caloric content of the ingested food, and wherein the control unit is adapted to determine the caloric content.
4. Apparatus according to claim 1, wherein the characteristic of the ingested food includes a chemical content of the ingested food, and wherein the control unit is adapted to determine the chemical content.
- 20 5. Apparatus according to claim 1, wherein the characteristic of the ingested food includes a nutritional content of the ingested food, and wherein the control unit is adapted to determine the nutritional content.
6. Apparatus according to claim 1, and comprising an operator unit, which is adapted to be disposed external to the subject and to transmit a control signal to the control unit.
- 25 7. Apparatus according to any one of claims 1-6, wherein the gastrointestinal sensor is adapted to generate a swallowing sensor signal responsive to swallowing by the subject.
- 30 8. Apparatus according to claim 7, wherein the gastrointestinal sensor is adapted to be placed at an esophageal site of the subject.

9. Apparatus according to claim 7, wherein the gastrointestinal sensor is adapted to be placed at a site of the stomach of the subject.

10. Apparatus according to claim 7, wherein the gastrointestinal sensor is adapted to be placed at a site of a throat of the subject.

5 11. Apparatus according to any one of claims 1-6, wherein the gastrointestinal sensor comprises a set of one or more fundic sensors, adapted to be coupled to a fundic site of a fundus of the stomach of the subject and to generate a fundic sensor signal responsive to a property of the fundus, and wherein the control unit is adapted to receive and analyze the fundic and antral sensor signals, and to determine, 10 responsive thereto, the characteristic of the ingested food.

12. Apparatus according to claim 11, wherein the fundic sensor set comprises one or more strain gauges.

13. Apparatus according to claim 11, wherein the antral sensor set comprises one or more strain gauges.

15 14. Apparatus according to claim 11, wherein the fundic sensor set comprises a set of fundic electrodes, adapted to generate a fundic electrode signal responsive to a property of the fundus, and wherein the antral sensor set comprises a set of antral electrodes, adapted to generate an antral electrode signal responsive to a property of the antrum, and wherein the control unit is adapted to receive and analyze the fundic 20 and antral electrode signals, and to determine, responsive thereto, the characteristic of the ingested food.

15. Apparatus according to claim 14, wherein the control unit is adapted to determine, responsive to an analysis of at least one of the electrode signals, an amount of the ingested food accumulated in a region of the stomach.

25 16. Apparatus according to claim 14, wherein the control unit is adapted to count, responsive to an analysis of at least one of the electrode signals, a number of meals ingested by the subject during a period of time.

17. Apparatus according to claim 14, wherein the antral electrode set comprises two antral electrodes, adapted to be coupled to two sites of the antrum, and wherein 30 the control unit is adapted to identify a measure of electrical impedance between the two sites of the antrum.

18. Apparatus according to claim 17, wherein the control unit is adapted to determine the characteristic of the ingested food, responsive to a change in the measure of electrical impedance.
19. Apparatus according to claim 14, wherein the fundic electrode set comprises two fundic electrodes, adapted to be coupled to two sites of the fundus, and wherein the control unit is adapted to identify a measure of electrical impedance between the two sites of the fundus.
20. Apparatus according to claim 19, wherein the control unit is adapted to determine the characteristic of the ingested food, responsive to a change in the measure of electrical impedance.
21. Apparatus according to claim 19, wherein the control unit is adapted to identify an increased measure of electrical impedance relative to a baseline value as indicative of eating.
22. Apparatus according to claim 19, wherein the control unit is adapted to identify a substantial return towards a baseline value of the measure of electrical impedance as indicative of a termination of eating.
23. Apparatus according to claim 19, wherein the control unit is adapted to identify an increase in the measure of electrical impedance as indicative of an onset of eating.
24. Apparatus according to claim 23, wherein the control unit is adapted to detect the onset of eating, responsive to the increase in the measure of electrical impedance being greater than about 5 ohms per centimeter of distance between the two sites of the fundus.
25. Apparatus according to claim 14, wherein the control unit is adapted to perform a calibration including measurement of a response of the fundic and antral electrode signals to ingestion by the subject of one or more test foods.
26. Apparatus according to claim 25, wherein the one or more foods includes one or more solid foods, and wherein the control unit is adapted to perform the calibration responsive to ingestion of the one or more solid foods.

27. Apparatus according to claim 25, wherein the one or more foods includes one or more liquid foods, and wherein the control unit is adapted to perform the calibration responsive to ingestion of the one or more liquid foods.
28. Apparatus according to claim 25, wherein the one or more foods includes one or more solid foods and one or more liquid foods, and wherein the control unit is adapted to perform the calibration responsive to ingestion of the one or more solid foods and the one or more liquid foods.
29. Apparatus according to claim 14, wherein the antral electrode set is adapted to generate the antral electrode signal responsive to an electrical potential change generated responsive to a contraction of a muscle of the antrum.
30. Apparatus according to claim 29, wherein the control unit is adapted to determine, responsive to an amplitude of the antral electrode signal, the characteristic of the ingested food.
31. Apparatus according to claim 29, wherein the control unit is adapted to determine, responsive to a frequency of the antral electrode signal, the characteristic of the ingested food.
32. Apparatus according to claim 29, wherein the control unit is adapted to determine, responsive to a spike energy per antral cycle of electrical activity, the characteristic of the ingested food.
33. Apparatus according to claim 29, wherein the control unit is adapted to determine, responsive to a duration of the antral electrode signal, the characteristic of the ingested food.
34. Apparatus according to claim 29, wherein the control unit is adapted to determine, responsive to a change in a rate of antral electrode signal events, the characteristic of the ingested food.
35. Apparatus according to claim 29, wherein the control unit is adapted to identify an increase in an amplitude of the antral electrode signal as indicative of an onset of a cephalic phase occurring in the subject.
36. Apparatus according to claim 29, wherein the control unit is adapted to identify an increase in an amplitude of the antral electrode signal as indicative of an onset of antral digestion.

37. Apparatus according to claim 29, wherein the control unit is adapted to identify a reduction in a rate of antral electrode signal events as indicative of an onset of antral digestion.
38. Apparatus according to claim 29, wherein the control unit is adapted to identify an increased amplitude of the antral electrode signal relative to a baseline value as indicative of antral digestion.
39. Apparatus according to claim 29, wherein the control unit is adapted to identify a reduced rate of antral electrode signal events relative to a baseline value as indicative of antral digestion.
- 10 40. Apparatus according to claim 29, wherein the control unit is adapted to identify a substantial return towards a baseline value of an amplitude of the antral electrode signal as indicative of a termination of antral digestion.
- 15 41. Apparatus according to claim 29, wherein the control unit is adapted to identify a substantial return towards a baseline value of a rate of antral electrode signal events as indicative of a termination of antral digestion.
42. Apparatus according to claim 14, wherein the control unit is adapted to determine the characteristic of the ingested food, responsive to a time delay between an onset of eating and an onset of a decreased rate of electrical events in the antrum.
- 20 43. Apparatus according to claim 42, wherein the control unit is adapted to determine the characteristic of the ingested food, responsive to the time delay and responsive to a threshold time delay.
44. Apparatus according to claim 42, wherein the control unit is adapted to determine, responsive to the time delay, an extent to which the ingested food includes solid food matter.
- 25 45. Apparatus according to claim 44, wherein the control unit is adapted to determine that the ingested food includes solid food matter, responsive to the time delay being more than about one minute.
46. Apparatus according to claim 45, wherein the control unit is adapted to determine that the ingested food includes predominantly solid food matter, responsive to the time delay being more than about 5 minutes.

47. Apparatus according to claim 42, wherein the control unit is adapted to determine, responsive to the time delay, an extent to which the ingested food includes liquid food matter.
48. Apparatus according to claim 47, wherein the control unit is adapted to determine that the ingested food includes liquid food matter, responsive to the time delay being less than about 5 minutes.
49. Apparatus according to claim 48, wherein the control unit is adapted to determine that the ingested food includes predominantly liquid food matter, responsive to the time delay being less than about one minute.
- 10 50. Apparatus according to claim 14, wherein the control unit is adapted to determine the characteristic of the ingested food, responsive to a time delay between an onset of eating and an onset of increased electrical activity in the antrum.
- 15 51. Apparatus according to claim 50, wherein the control unit is adapted to determine the characteristic of the ingested food, responsive to the time delay and responsive to a threshold time delay.
52. Apparatus according to claim 50, wherein the control unit is adapted to determine, responsive to the time delay, an extent to which the ingested food includes solid food matter.
- 20 53. Apparatus according to claim 52, wherein the control unit is adapted to determine that the ingested food includes solid food matter, responsive to the time delay being more than about one minute.
54. Apparatus according to claim 53, wherein the control unit is adapted to determine that the ingested food includes predominantly solid food matter, responsive to the time delay being more than about 5 minutes.
- 25 55. Apparatus according to claim 50, wherein the control unit is adapted to determine, responsive to the time delay, an extent to which the ingested food includes liquid food matter.
56. Apparatus according to claim 55, wherein the control unit is adapted to determine that the ingested food includes liquid food matter, responsive to the time delay being less than about 5 minutes.
- 30

57. Apparatus according to claim 56, wherein the control unit is adapted to determine that the ingested food includes predominantly liquid food matter, responsive to the time delay being less than about one minute.

58. Apparatus according to claim 14, wherein the fundic electrode set is adapted to 5 generate the fundic electrode signal responsive to an electrical potential change generated responsive to a contraction of a muscle of the fundus.

59. Apparatus according to claim 58, wherein the control unit is adapted to determine, responsive to an amplitude of the fundic electrode signal, the characteristic of the ingested food.

10 60. Apparatus according to claim 58, wherein the control unit is adapted to determine, responsive to a frequency of the fundic electrode signal, the characteristic of the ingested food.

15 61. Apparatus according to claim 58, wherein the control unit is adapted to determine, responsive to a duration of the fundic electrode signal, the characteristic of the ingested food.

62. Apparatus according to claim 58, wherein the control unit is adapted to determine, responsive to a change in a rate of fundic electrode signal events, the characteristic of the ingested food.

20 63. Apparatus according to claim 58, wherein the control unit is adapted to identify an increased amplitude of the fundic electrode signal relative to a baseline value as indicative of eating.

64. Apparatus according to claim 58, wherein the control unit is adapted to identify an increased frequency of the fundic electrode signal relative to a baseline value as indicative of eating.

25 65. Apparatus according to claim 58, wherein the control unit is adapted to identify a substantial return towards a baseline value of an amplitude of the fundic electrode signal as indicative of a termination of eating.

66. Apparatus according to claim 58, wherein the control unit is adapted to identify a substantial return towards a baseline value of a frequency of the fundic 30 electrode signal as indicative of a termination of eating.

67. Apparatus according to claim 58, wherein the control unit is adapted to identify an increase in an amplitude of the fundic electrode signal as indicative of an onset of eating.

68. Apparatus according to claim 67, wherein the control unit is adapted to detect 5 the onset of eating responsive to the increase in the amplitude of the fundic electrode signal being greater than about 20 percent.

69. Apparatus according to claim 58, wherein the control unit is adapted to identify an increase in a frequency of the fundic electrode signal as indicative of an onset of eating.

10 70. Apparatus according to claim 69, wherein the control unit is adapted to detect the onset of eating, responsive to the increase in the frequency being greater than about 10 percent.

15 71. Apparatus according to any one of claims 1-6, wherein the control unit comprises a memory, adapted to store a result of the analysis performed by the control unit.

72. Apparatus according to claim 71, wherein the memory is adapted to upload the stored result to an external computer.

73. Apparatus according to claim 72, wherein the memory is adapted to upload by using a wireless communications link.

20 74. Apparatus according to any one of claims 1-6, and comprising a supplemental sensor adapted to be placed at a site of the subject and to convey a supplemental sensor signal to the control unit.

75. Apparatus according to claim 74, wherein the control unit is adapted to receive and analyze the supplemental sensor signal, and to determine, responsive thereto, the 25 characteristic of the ingested food.

76. Apparatus according to claim 74, wherein the control unit is adapted to receive and analyze the supplemental sensor signal, and to determine, responsive thereto, an onset of eating by the subject.

77. Apparatus according to claim 74, wherein the control unit is adapted to receive 30 and analyze the supplemental sensor signal, and to determine, responsive thereto, eating by the subject.

78. Apparatus according to claim 74, wherein the control unit is adapted to receive and analyze the supplemental sensor signal, and to determine, responsive thereto, a termination of eating by the subject.

79. Apparatus according to claim 74, wherein the supplemental sensor comprises 5 an electrode.

80. Apparatus according to claim 74, wherein the supplemental sensor comprises a pH sensor.

81. Apparatus according to claim 74, wherein the supplemental sensor comprises a blood sugar sensor.

10 82. Apparatus according to claim 74, wherein the supplemental sensor comprises an ultrasound transducer.

83. Apparatus according to claim 74, wherein the supplemental sensor comprises a mechanical sensor.

15 84. Apparatus according to claim 74, wherein the supplemental sensor is adapted to be placed at a gastrointestinal site of the subject.

85. Apparatus according to claim 84, wherein the supplemental sensor is adapted to be placed at an esophageal site of the subject.

86. Apparatus according to claim 84, wherein the supplemental sensor is adapted to be placed at a site of the stomach of the subject.

20 87. Apparatus according to claim 84, wherein the supplemental sensor is adapted to be placed at a site of a throat of the subject.

88. Apparatus according to any one of claims 1-6, wherein the control unit comprises a memory, adapted to store a schedule of allowed food ingestion, wherein the apparatus comprises an operator unit, which is adapted to be disposed external to 25 the subject, and wherein the operator unit is adapted to generate an external cue when the analysis performed by the control unit is indicative of the subject not eating in accordance with the ingestion schedule.

89. Apparatus according to claim 88, wherein the external cue includes a visual cue, and wherein the operator unit is adapted to generate the visual cue.

90. Apparatus according to claim 88, wherein the external cue includes an audio cue, and wherein the operator unit is adapted to generate the audio cue.

91. Apparatus according to claim 88, wherein the operator unit comprises a user override, adapted to be used by the subject and adapted to disable the cue.

5 92. Apparatus according to claim 88, wherein the operator unit is adapted to modify the schedule stored in the memory.

93. Apparatus according to claim 92, wherein the operator unit is adapted to modify the schedule responsive to information obtained by the operator unit.

10 94. Apparatus according to claim 93, wherein the operator unit is adapted to modify the schedule responsive to information obtained by the operator unit via a wireless communications link.

15 95. Apparatus according to any one of claims 1-6, and comprising a set of one or more current-application electrodes, adapted to be coupled to a tissue of the subject, and wherein the control unit is adapted to drive a current, responsive to the analysis, through the set of current-application electrodes into the tissue.

96. Apparatus according to claim 95, wherein the current-application electrode set is adapted to be placed at an aural site of the subject.

97. Apparatus according to claim 95, wherein the current-application electrode set is adapted to be placed at an esophageal site of the subject.

20 98. Apparatus according to claim 95, wherein the current-application electrode set is adapted to be placed at a site of the stomach of the subject.

99. Apparatus according to claim 95, wherein the control unit is adapted to drive the current into the tissue responsive to the characteristic of the ingested food.

100. Apparatus according to claim 95, wherein the control unit is adapted to apply a 25 pacing signal to a rectus abdominus muscle of the subject.

101. Apparatus according to claim 95, wherein the control unit is adapted to drive the current into the tissue responsive to a time of the subject eating.

102. Apparatus according to claim 95, wherein the control unit is adapted to configure the current such that driving the current induces gastric dysrhythmia.

103. Apparatus according to claim 95, wherein the control unit is adapted to configure the current such that driving the current disrupts coupling of gastric mechanical activity and gastric electrical activity of the subject.

104. Apparatus according to claim 95, wherein the control unit is adapted to 5 configure the current such that driving the current induces a sensation of discomfort in the subject.

105. Apparatus according to claim 95, wherein the control unit is adapted to configure the current such that driving the current induces a sensation of nausea in the subject.

10 106. Apparatus according to claim 95, wherein the control unit is adapted to configure the current such that driving the current induces a sensation of vertigo in the subject.

15 107. Apparatus according to claim 95, wherein the control unit is adapted to drive the current-application electrode set to apply an Excitable-Tissue Control (ETC) signal to the tissue.

108. Apparatus according to claim 107, wherein the control unit is adapted to drive the current-application electrode set to apply a stimulatory pulse at a site of application of the ETC signal.

20 109. Apparatus according to claim 107, wherein the control unit is adapted to drive the current-application electrode set to apply a stimulatory pulse to tissue at a site other than a site of application of the ETC signal.

110. Apparatus according to claim 107, wherein the control unit is adapted to drive the current-application electrode set to apply the ETC signal in order to increase an aspect of contraction of the tissue.

25 111. Apparatus according to claim 107, wherein the control unit is adapted to drive the current-application electrode set to apply the ETC signal in order to cause tissue contraction in a first portion of the stomach of the subject, and stretching of a stretch receptor of the stomach in a second portion of the stomach.

30 112. Apparatus according to claim 107, wherein the control unit is adapted to drive the current-application electrode set to apply the ETC signal in order to increase a

contraction strength of tissue in a vicinity of a stretch receptor of the stomach of the subject, so as to increase a sensation of satiation of the subject.

113. Apparatus according to claim 107, wherein the control unit is adapted to drive the current-application electrode set to apply the ETC signal to the tissue so as to 5 enhance movement of chyme from a fundus to the antrum of the stomach of the subject.

114. Apparatus according to claim 95, wherein the control unit comprises a memory, adapted to store a schedule of allowed food ingestion, and wherein the control unit is adapted to withhold driving the current when the analysis performed by 10 the control unit is indicative of the subject eating in accordance with the ingestion schedule.

115. Apparatus according to claim 114, wherein the ingestion schedule includes types of foods and associated amounts permitted during a time period, and wherein the control unit is adapted to withhold driving the current when the analysis is 15 indicative of the subject eating in accordance with the ingestion schedule.

116. Apparatus according to claim 114, wherein the ingestion schedule includes a number of meals permitted during a time period, and wherein the control is adapted to withhold driving the current when the analysis is indicative of the subject eating in accordance with the ingestion schedule.

20 117. Apparatus according to claim 114, wherein the ingestion schedule includes an amount of food permitted at a certain meal, and wherein the control is adapted to withhold driving the current when the analysis is indicative of the subject eating in accordance with the ingestion schedule.

118. Apparatus according to claim 114, wherein the memory is adapted to 25 download a new schedule from an external computer.

119. Apparatus according to claim 114, and comprising an operator unit, which is adapted to be disposed external to the subject and to transmit a control signal to the control unit.

30 120. Apparatus according to claim 119, wherein the operator unit comprises a user override, adapted to be used by the subject and adapted to withhold driving the current.

121. A method for analyzing gastric function of a stomach of a subject, comprising:
sensing a property of a gastrointestinal tract of the stomach;
sensing a property of an antrum of the stomach;
analyzing the property of the gastrointestinal tract and the property of the
5 antrum; and
determining, responsive to the analysis, a characteristic of a food ingested by
the subject.

122. A method according to claim 121, wherein the characteristic of the ingested
food includes a caloric content of the ingested food, and wherein the method
10 comprises determining the caloric content.

123. A method according to claim 121, wherein the characteristic of the ingested
food includes a chemical content of the ingested food, and wherein the method
comprises determining the chemical content.

124. A method according to claim 121, wherein the characteristic of the ingested
15 food includes a nutritional content of the ingested food, and wherein the method
comprises determining the nutritional content.

125. A method according to claim 121, and comprising receiving a control signal
from a source outside of the subject.

126. A method according to claim 121, and comprising storing an ingestion
20 schedule and generating an external cue when the analysis performed is indicative of
the subject not eating in accordance with the ingestion schedule.

127. A method according to any one of claims 121-126, wherein sensing the
property of the gastrointestinal tract comprises sensing a property of a fundus of the
stomach.

25 128. A method according to claim 127, wherein sensing the property of the fundus
comprises sensing an electrical current in the fundus, and wherein sensing the
property of the antrum comprises sensing an electrical current in the antrum.

129. A method according to claim 128, wherein sensing the current in the fundus
comprises sensing a current indicative of a measure of electrical impedance between
30 two sites of the fundus.

130. A method according to claim 128, wherein sensing the current in the antrum comprises sensing a current generated responsive to a contraction of a muscle of the antrum.

131. A method according to claim 128, wherein determining the characteristic of 5 the ingested food comprises determining the characteristic responsive to a time delay between an onset of eating and an onset of a decreased rate of electrical events in the antrum.

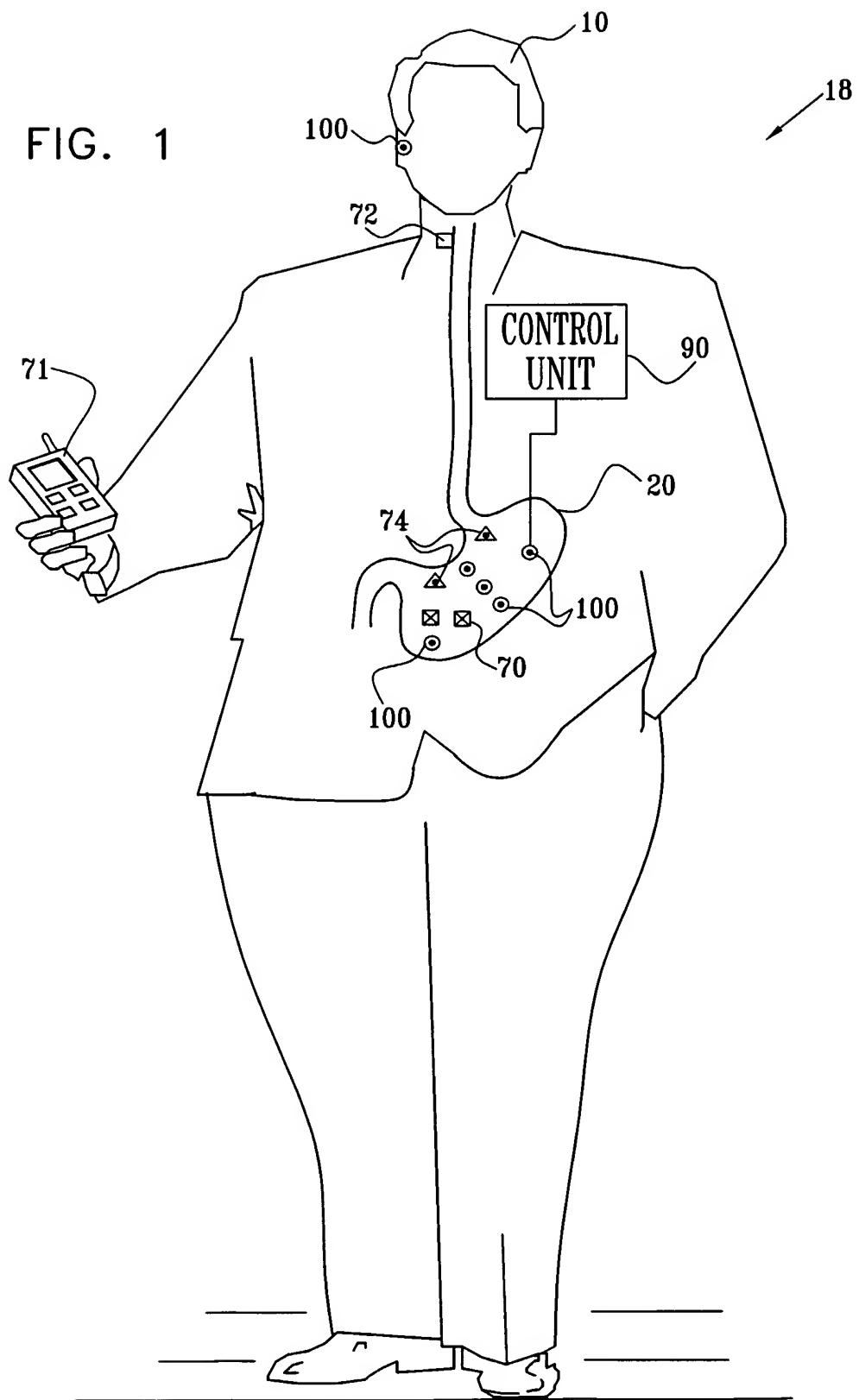
132. A method according to claim 128, wherein determining the characteristic of 10 the ingested food comprises determining the characteristic responsive to a time delay between an onset of eating and an onset of increased electrical activity in the antrum.

133. A method according to claim 128, wherein sensing the current in the fundus comprises sensing a current generated responsive to a contraction of a muscle of the fundus.

134. A method according to any one of claims 121-126, and comprising driving a 15 current into tissue of the subject responsive to the analysis.

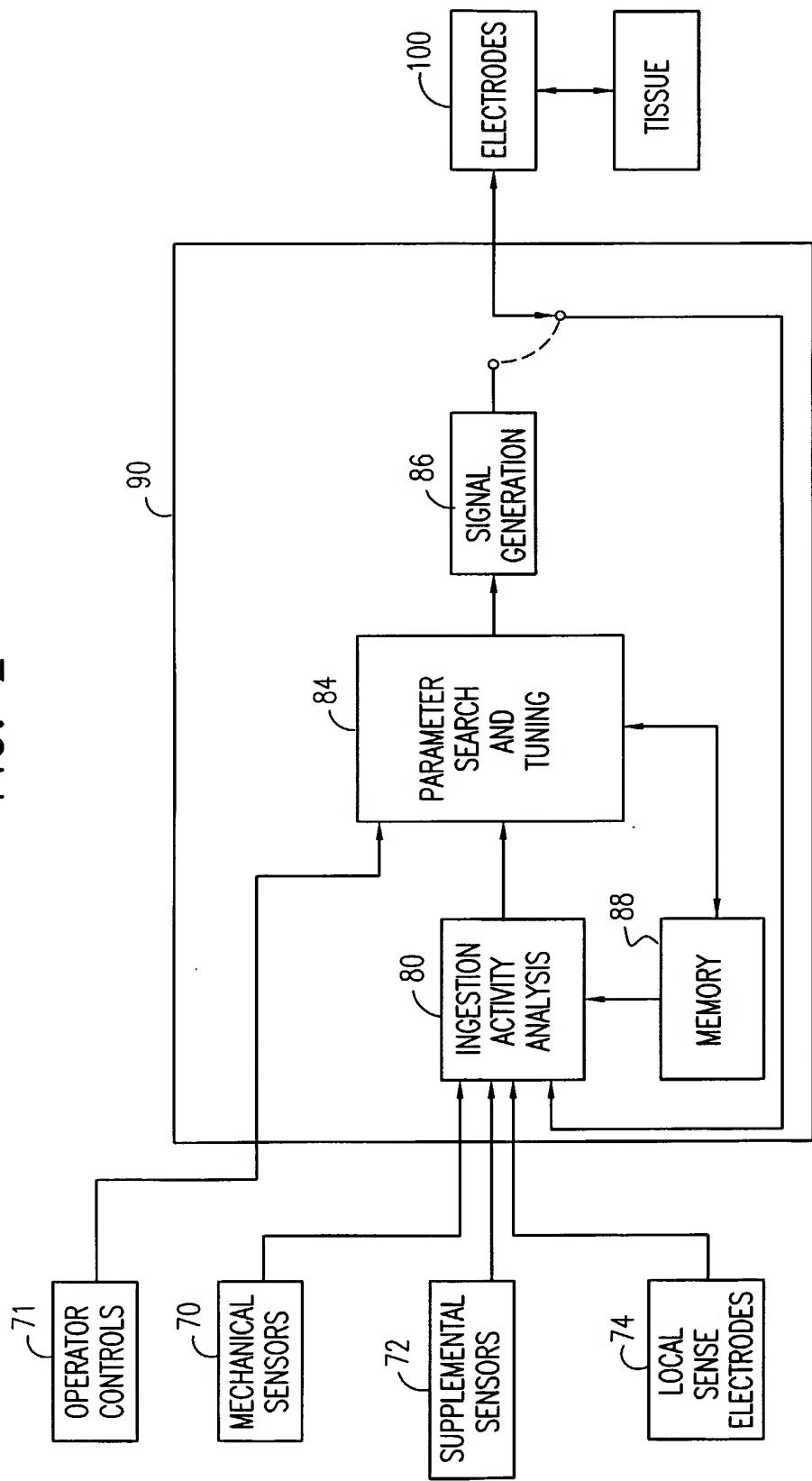
1/11

FIG. 1



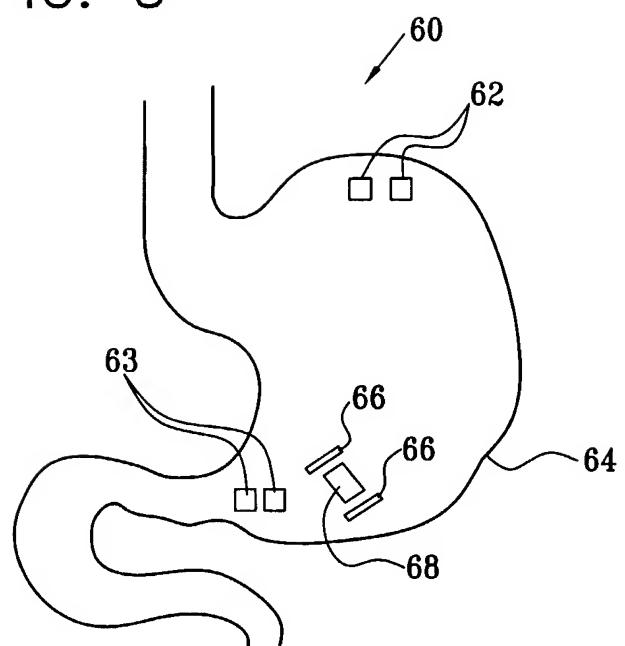
2/11

FIG. 2



3/11

FIG. 3



4/11

FIG. 4

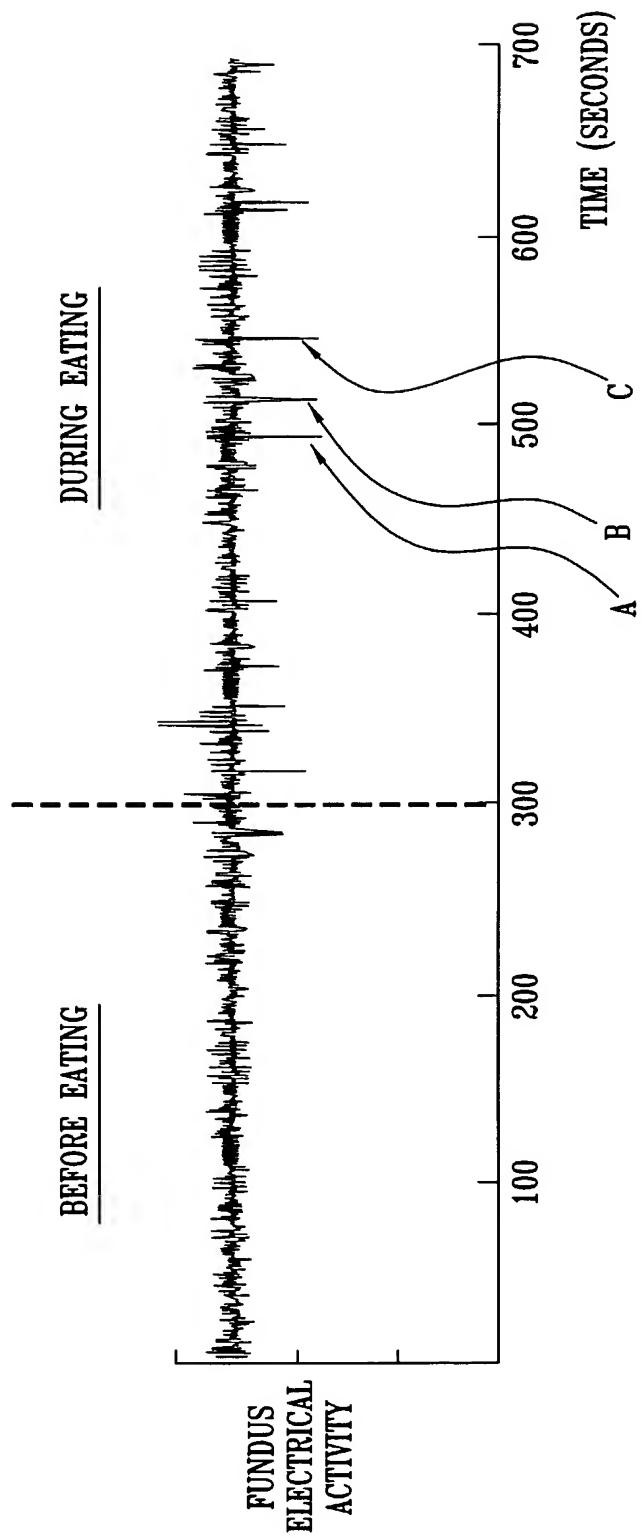
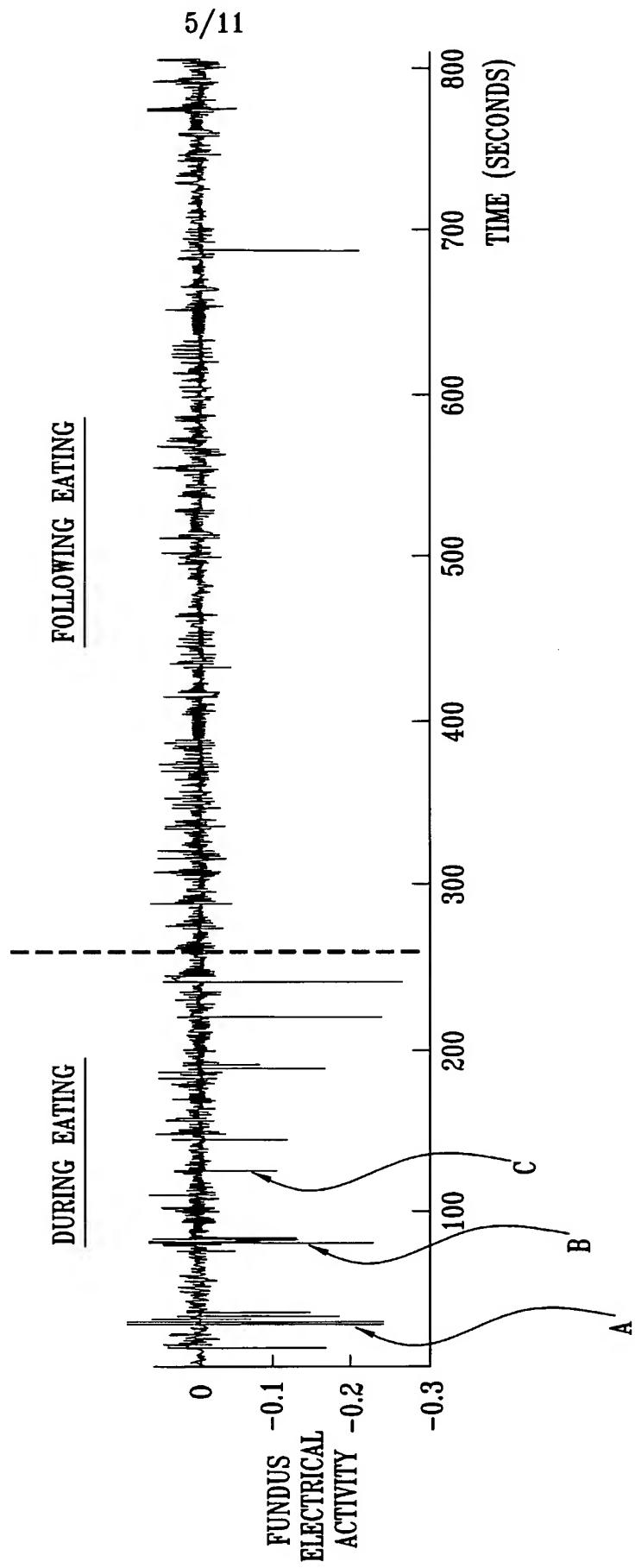
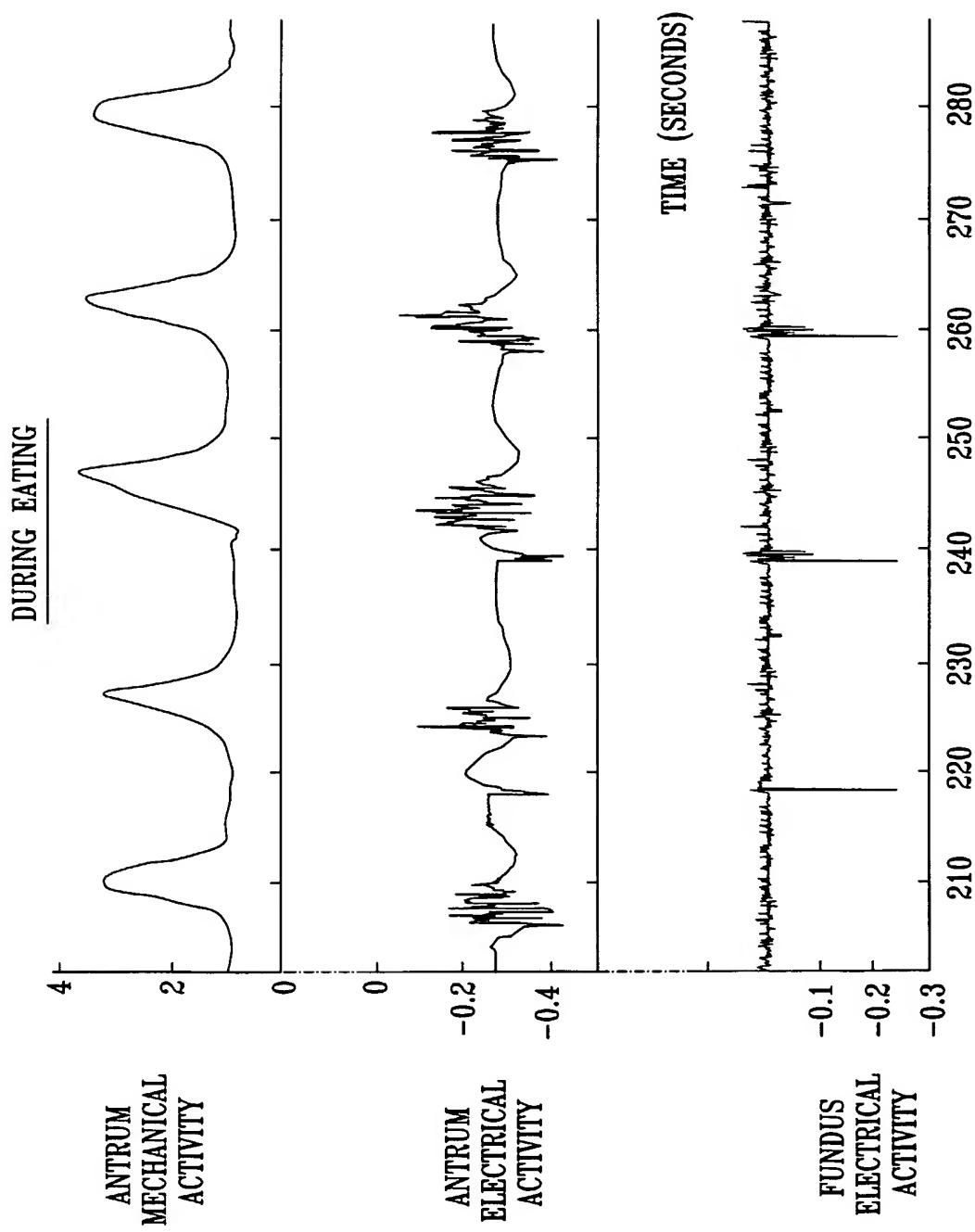


FIG. 5A



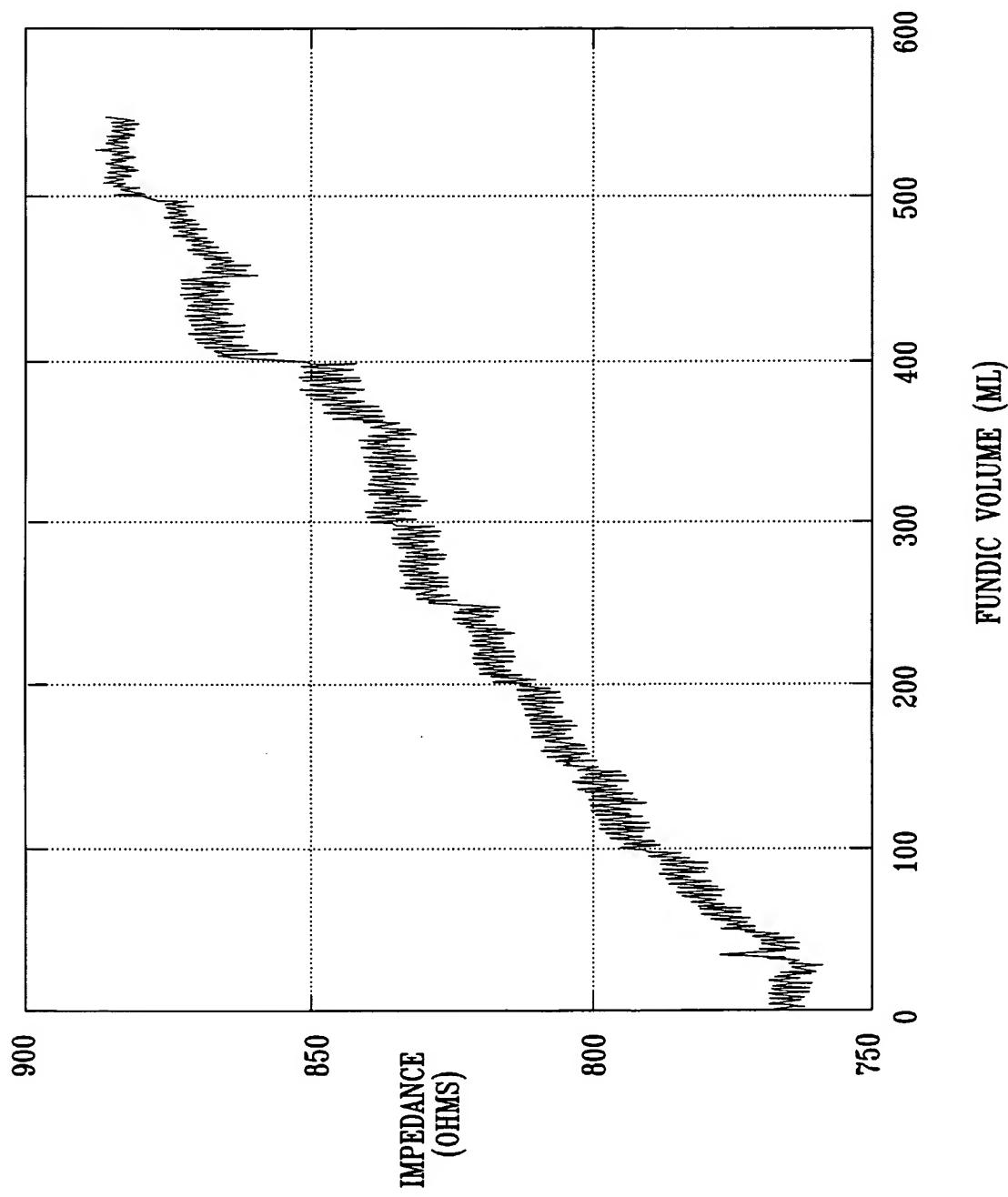
6/11

FIG. 5B



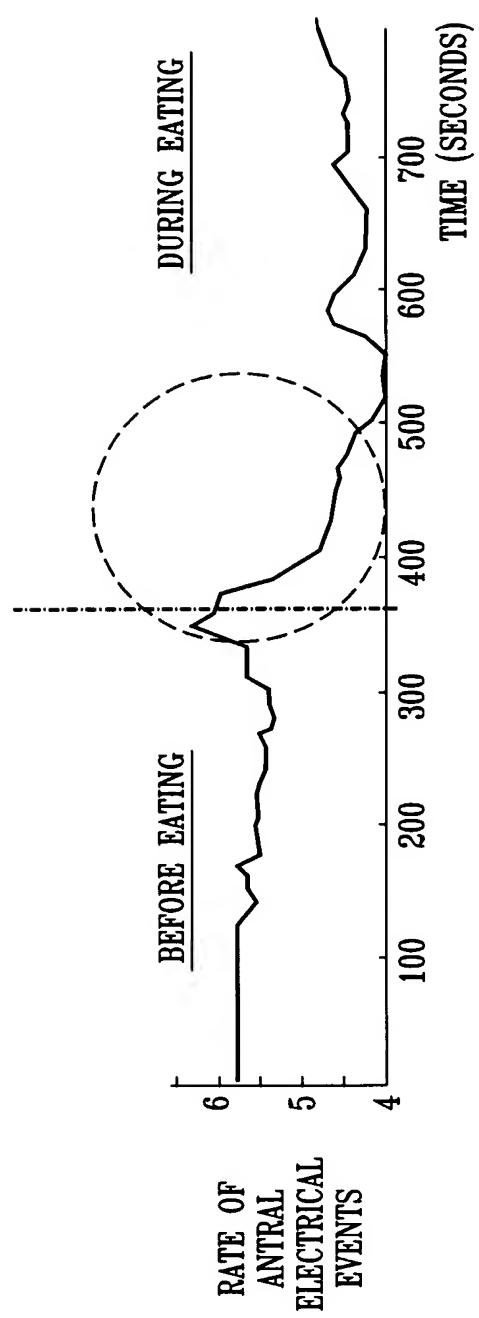
7/11

FIG. 6



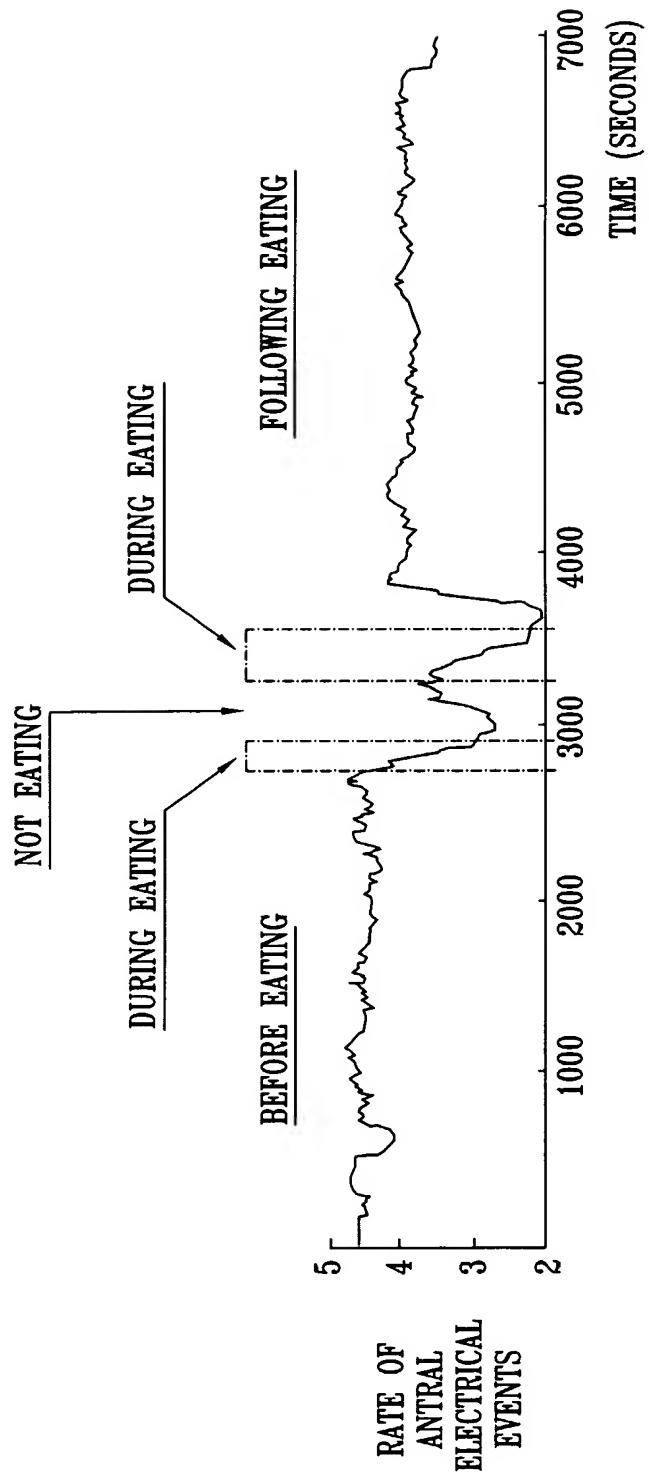
8/11

FIG. 7

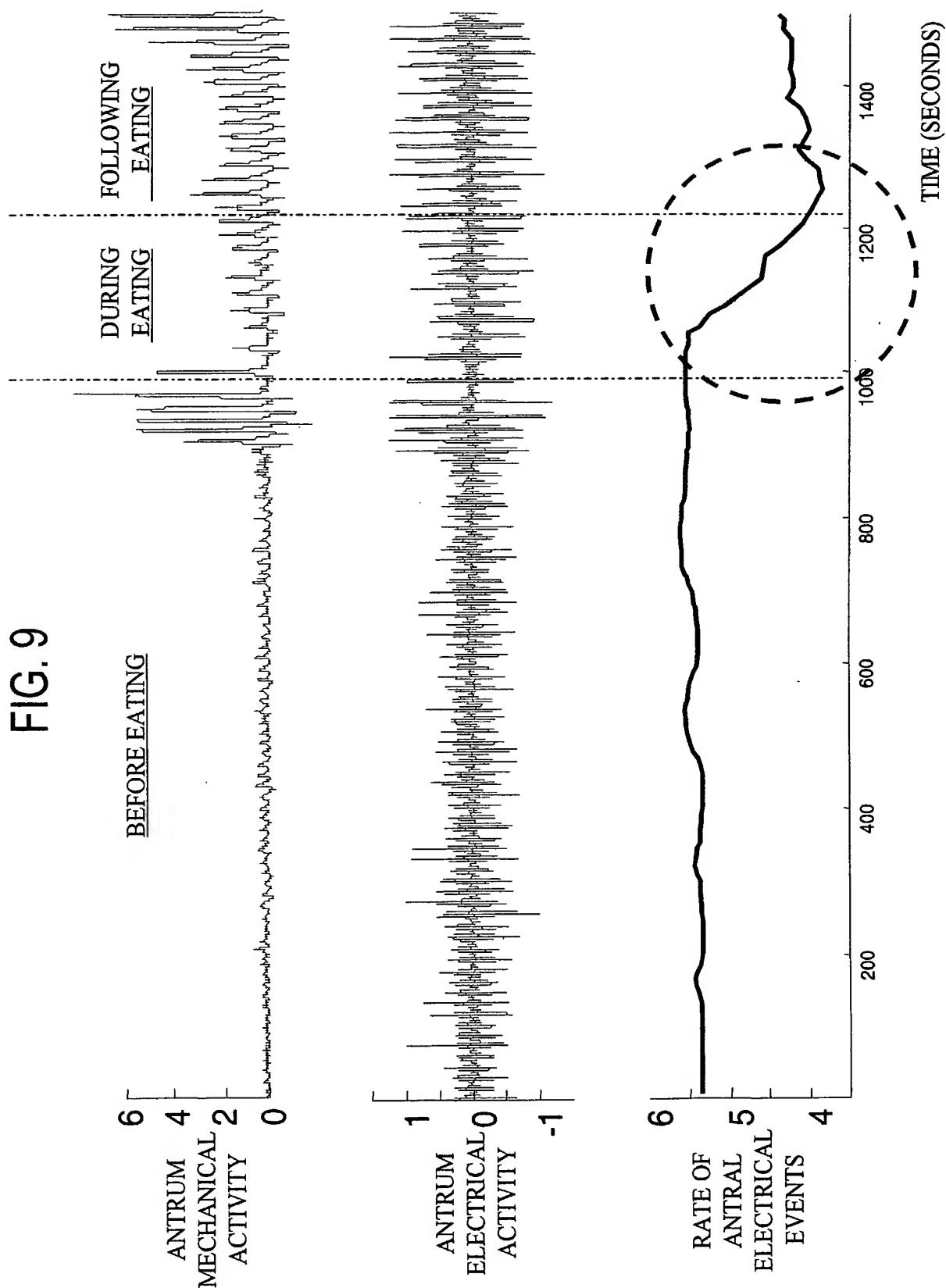


9/11

FIG. 8



10/11



11/11

FIG. 10

